REMARKS

In the Action, claims 1-3 are rejected, and claims 4-7 are objected to. In response, claims 2, 6 and 15 are amended to correct matters of form, and new claims 18-21 are added. These amendments are supported by the specification as originally filed.

In view of the following comments, reconsideration and allowance are requested.

Claims 4-17 are Improperly Withdrawn

On page 2 of the Action, claims 4-17 are objected to as allegedly being in improper multiple dependent form. Applicants' representative advised the Examiner by voicemail on July 7, 2011 that a Preliminary Amendment had been filed to remove the improper multiple dependent claims. The Preliminary Amendment was filed simultaneously with this application on May 12, 2006. The Preliminary Amendment is of record in this application and appears of record in PAIR. Thus, Applicants respectfully submit that the Examiner did not examine the current set of claims and that the claims are in proper form.

Since the claims were properly amended to remove the multiple dependencies at the time of filing, the claims are in proper form. Accordingly, Applicants request examination of claims 1-17.

The Rejections

Claims 1-3 are rejected over the combination of six cited references. Specifically, claims 1-3 are rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,688,491 to Shahidi, in view of U.S. Patent No. 5,628,986 to Sanker et al., the passage from the *Source Book of Flavors* by Heath, the passage from *Food and Chemical Toxicology* regarding

dimethoxybenzene, the passage from *Taste and Smell* from medicinenet.com, the passage from *The Good Scents Company*, and U.S. Patent No. 5,795,616 to Greenberg.

Claim 1 is directed to a mixture that requires four compounds which can contain an optional fifth compound. The fact that the Examiner requires the combination of seven references to reject a claim reciting four compounds is evidence of the non-obviousness of the claimed mixture.

Shahidi has no relation to the claimed invention. Shahidi only discloses oral compositions to provide anti-caries, anti-plaque and anti-gingivitis benefits. Shahidi does not disclose any of the claimed compounds. Simply because Shahidi may disclose a flavorant does not render the claimed combination obvious to one of ordinary skill in the art.

Sanker et al. is cited for disclosing an oral composition containing dihydroanethole. Sanker et al. does not disclose the other claimed compounds and provides no suggestion to one skilled in the art to combine the compounds in the manner of the claimed invention. Heath is cited for disclosing o-anisaldehyde and 2-hydroxyacetophenone. The *Food and Chemical Toxicology* is cited for disclosing m-dimethoxybenzene.

Medicinenet.com is cited simply to show that taste and smell are sensations that result when nerve receptors in the mouth detect molecules. This has no relation to the claimed combination of compounds and clearly provides no suggestion to one of ordinary skill in the art to combine the compounds in the manner of the claimed invention.

Identifying four of the claimed compounds separately in the art does not establish the obviousness of combining the compounds in the claimed manner. The Examiner provides no rationale for the position that it would have been obvious to combine the compounds in the claimed manner simply because the compounds are known to exist individually. The Examiner

must provide some reasoning to combine the compounds of the cited art in the manner of the claimed invention. The Examiner has not provided an adequate basis to show that one skilled in the art would have a reason to combine the compounds in the claimed invention or that combining the compounds would provide a predictable result.

As recognized in the Action, the invention is directed to a mixture of compounds that provide a wintergreen flavor or odor. The Examiner provides no basis for the position that it would have been obvious to combine the compounds in the claimed manner with an expectation that the combination would have a wintergreen flavor or odor. Moreover, the Examiner has not provided an adequate reason to combine compounds that have no wintergreen odor or flavor to obtain a mixture that does have a wintergreen odor or flavor.

The Action asserts that the claimed combination would "naturally contain a wintergreen odor or flavor" due to the presence of 2-hydroxyacetophenone. The Action asserts that 2-hydroxyacetophenone inherently exhibits a wintergreen odor because salicylaldehyde exhibits a cinnamon-wintergreen flavor and 2-hydroxypropiophenone is described as containing a wintergreen note as disclosed in Greenberg. This position is based entirely on speculation and is not supported by any evidence.

It is well established that small changes in the chemical structure of a compound can have dramatic effects on the flavor and odor of a compound. For example, the attached copy of *Angew. Chem. Int. Ed.*, C.S. Sell, 2006, 45, 6254-6261 (Exhibit 1) states that the prediction of an odor of a novel molecule is a statistical exercise. Thus, the odor of a compound or mixture of compounds cannot be predicted based on the structure of the compound. As stated on page 6255, second column, "One phenomenon that seriously disrupts attempts to correlate odor

properties with molecular structure is that a given structural modification can induce a dramatic change in odor properties in one situation whilst having little or no effect in another".

The Action has not established that 2-hydroxyacetophenone exhibits a wintergreen odor. Furthermore, this position is clearly contrary to the evidence presented in the present specification and Sell demonstrating the unpredictability of odors based on the structure of the compound. As specifically disclosed on page 5 of the present specification, 2-hydroxyacetophenone also referred to as 1-(2-hydroxyphenyl)-ethanone as Compound D exhibits a "sharp, cherry-almond-hawthorne-hay, cinnamon, naphthyl, cherry pit, coumarin, phenolic, tobacco and honey sensory characteristic". The Action provides no evidence to contradict the evidence of record. Thus, the assertion that the 2-hydroxyacetophenone will inherently exhibit a wintergreen odor either alone or in combination with the three additional claimed compounds is not supported by any evidence of record, is based on speculation and is contrary to the statement in the specification.

At www.thegoodscentcompany.com, 2'-hydroxyacetophenone (attached as Exhibit 2) describes the odor and taste as "naphthyl, cinnamon, cherry pit, coumarin, phenolic, tobacco and honey" and "phenolic, sharp, benzaldehyde, cherry pit, tropical, melon with a tobacco afternote" based on publications by Gerard Mosciano. Salicylaldehyde (Exhibit 3) is described by Gerard Mosciano as having an odor of "medical spicy cinnamon-wintergreen like cooling note". Thus, the same expert clearly distinguishes the odors and provides clear evidence that the odor and/or taste perception of the two compounds are not the same. One skilled in the art uses the descriptor "wintergreen" only when appropriate. Thus, it would be clear to one skilled in the art that 2'-hydroxyacetophenone does not have a wintergreen odor or taste.

Furthermore, the Action fails to provide any basis for the assertion that it would have been obvious to combine 1-methyl-4-propyl-benzene, 2-methoxybenzaldehyde and 1,3-dimethoxybenzene to the 2-hydroxyacetophenone to impart a wintergreen flavor or odor. The Action provides no basis for the assertion that it would have been obvious to add the other three compounds A, B and C to a compound that according to the Examiner already exhibits a wintergreen flavor. The existence of the compounds in the literature does not establish the obviousness to combine the compounds of the claimed combination when one skilled in the art would have no apparent reason to make the combination.

For the reasons discussed above, the art of record provides no suggestion to one skilled in the art to combine the compounds A, B, C and D in the manner of the claimed invention. The Action provides no rationale or reasonable basis to assert that it would have been obvious to combine the compounds in the manner of the claimed invention. The art of record provides no reasonable expectation that the compounds of claim 1 can be combined to provide a wintergreen flavor or odor as in claim 2. The basis for the rejection of claim 3 is unclear. The rejection is based on the position that Shahidi discloses a composition where the flavoring agent is present in an amount of 0.01% to about 5.0%. Shahidi does not disclose any of the compounds of claim 1. Furthermore, Shahidi does not disclose a combination of flavoring agents in any particular ratio. Therefore, Shahidi clearly provides no suggestion to one skilled in the art to combine compounds that are neither disclosed nor suggested in Shahidi in the claimed amounts. The Action clearly fails to establish prima facie obviousness of claim 3.

For the reasons discussed above, the combination of the seven cited references does not establish prima facie obviousness of the claimed mixture of compounds. Accordingly, the claims are submitted as being allowable over the art of record.

Respectfully submitted,

Garrett V. Davis
Reg. No. 32,023

Roylance, Abrams, Berdo & Goodman, L.L.P.
1300 19th Street, N.W., Suite 600
Washington, D.C. 20036-1649
(202) 659-9076

Dated: Sept 30, 2011

DOI: 10.1002/anie.200600782

Structure–Odor Relationships

On the Unpredictability of Odor

*C. S. Sell**

Keywords:
fragrances · olfaction · receptors · structure–activity relationships

The relationship between molecular structure and odor has fascinated and puzzled chemists for more than a century. Despite a great deal of research on structure–odor relationships, prediction of the odor of a novel molecule remains a statistical exercise and models only provide a probability of the character, threshold, and intensity. Surprises are still commonplace, and serendipity continues to be an important factor in the discovery of novel fragrant molecules. Recent advances in our understanding of the mechanism of olfaction provide an explanation for this and suggest that our ability to predict odor properties of molecules will not improve significantly in the near future.

1. Introduction

The search to correlate the molecular structure and the odor character of a chemical compound has a long recorded history. In ancient Greece, the proponents of Democritus' atomic theory proposed that the atoms of sweet-smelling substances had smooth surfaces whereas those of acidic materials had sharp points that pricked and irritated the nose. Since the development of synthetic organic chemistry in the 19th century, chemists have sought a clearer understanding of the relationship between molecular structure and the odor of a molecule, largely with the intention to design novel molecules with desirable odor properties.

However, this search for understanding has proved to be a very difficult task. There are many puzzling observations that often have no simple or obvious explanation. For example, on one hand, quite different molecules can have similar odors, whereas, on the other hand, similar molecules can have dissimilar odors. Thus, despite the significant differences in their structures, muscone (**1**),[1] musk ketone (**2**),[2] Traseolide (**3**),[3] and Helvetolide (**4**)[4] all have similar musk odors (Figure 1), whereas the two very similar structures **5** and **6** have very different organoleptic properties: **5** has an intense urinous character while **6** is odorless.[5]

Sometimes, the functional group present in an odorant is all-important. For example, the ester group is often associated with a fruity character.[6] Thus, both Fruitate (**7**)[7] and Manzanate (**8**)[8] have distinctly fruity odors despite the differences in size and structural complexity between them (Figure 2). However, in other cases, the functional group seems unimportant: for example, structures **9**–**12** all have camphoraceous odors.[9]

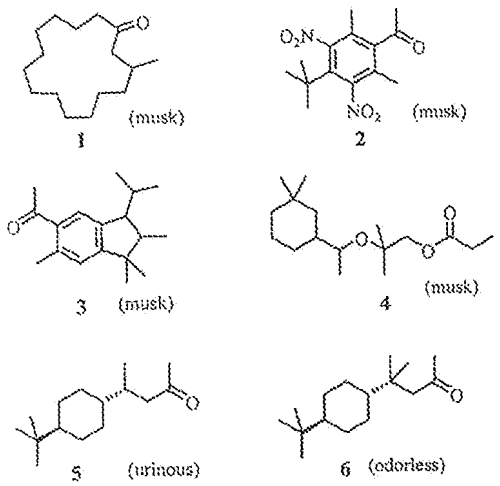


Figure 1. Different molecules, similar odors; and vice versa.

In many instances factors such as these can be brought together in triads, where the odd molecule out in structural terms is *not* the odd one out in odor. For example, of the structures **13**–**15** the last, **15**, is the odd one out in chemical terms as it is an alicyclic alcohol, whereas the other two, namely **13** and **14**, are both cinnamaldehyde derivatives (Figure 3). However, in terms of odor, it is α-methylcinna-

[*] Dr. C. S. Sell
Quest International
Willesborough Road
Ashford, Kent, TN24 0LT (UK)
Fax: (+44) 1233-644-738
E-mail: charles.sell@questintl.com

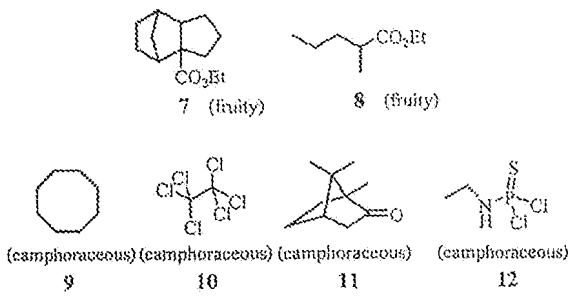


Figure 2. Role of the functional group.

maldehyde (**14**) which is the odd one out as it has a cinnamon odor[10] whereas Lilial (**13**, also known as Lily Aldehyde and Lilestralis)[11] and Florosa or Florol (**15**)[8] both have muguet (lily-of-the-valley) odors. As stated above, the ester group is usually associated with fruity scents, but *tert*-amyl acetate (**17**) has an odor which is much closer to that of camphor (**11**) than to the fruity, banana–pear scent of its isomer, *n*-amyl acetate (**16**; Figure 3).[6]

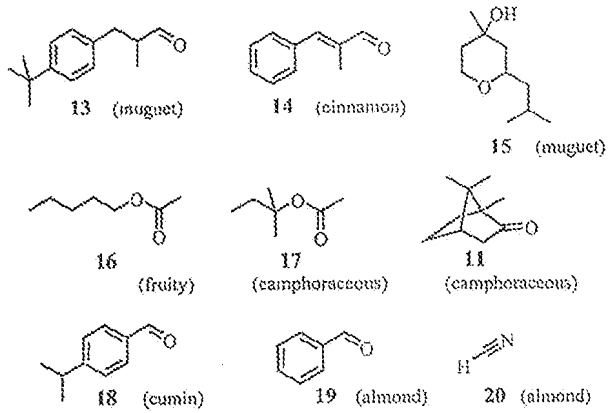


Figure 3. Triads of molecules in which the odd one out structurally is not necessarily the odd one out in odor.

Perhaps the most bizarre and best known of these triads is that involving structures **18**–**20**. Cuminaldehyde (**18**),[12] as its name suggests, smells of cumin, whereas benzaldehyde (**19**)[13] and hydrogen cyanide (**20**)[14] both smell of almond. Some theories have been proposed to account for the similarity in odor between **19** and **20**, for example, by invoking oligomerization of HCN in the receptor binding site.[15] However, the explanation is surely more likely to lie in higher-order neuroprocessing.[16]

Charles S. Sell completed his BSc and MSc (James Grimshaw) degrees at Queen's University (Belfast) and then took up a scholarship at the Australian National University, where he completed his PhD in the group of Arthur Birch in 1974. After postdoctoral fellowships with Albert Eschenmoser (ETH Zürich) and Bernard Golding (University of Warwick), he joined Quest International. His interests since then have involved both discovery and process research in fragrance and flavor chemistry. His main research interests are terpenoid chemistry and the mechanism of olfaction.

2. Structure–Odor Models

Over the last century, many theories have been proposed relating to the primary events in olfaction and to relationships between molecular structure and odor. The review by Rossiter[17] gives an excellent summary of these theories. However, the prediction of odor remains a statistical exercise. For example, Chastrette and De Sainte Laumer developed a model based on a neural network for the prediction of the musk odor of nitrobenzene derivatives.[18] Their model gave results that were correct in 77% of test materials. Similarly, Bersuker et al. developed a model for musk activity based on an electron-topological approach.[19] Their results were impressive, yet 15 of their set of 362 materials were incorrectly predicted.

Most structure–odor models are concerned with the character of the odor. However, the commercially important parameters of detection threshold, recognition threshold, and superthreshold intensity of odorants have received much less attention, partly because of the difficulty[20] and cost of measurement of these parameters and/or because such models are even more difficult to construct. Nevertheless, detection threshold models are beginning to appear and examples include studies by Kraft on materials with marine[21] and musk[22] odor characters.

In his review of the subject, Weyerstahl concluded: "*Despite numerous excellent studies during the last 30 years the area of structure–odour relationships remains rather confusing.*"[23]

3. The Effect of Structural Modifications

One phenomenon that seriously disrupts attempts to correlate odor properties with molecular structure is that a given structural modification can induce a dramatic change in odor properties in one situation whilst having little or no effect in another. The following list of examples serves to illustrate that this is a general phenomenon that is applicable across a wide range of structural modifications and not just a few isolated instances.

The majority of odorants contain only one strongly polar function in the molecular structure. It is generally believed that this polar group will form a hydrogen bond or some other dipolar attachment to a polar site on an olfactory receptor, with the remainder of the molecule occupying a hydrophobic space in the receptor. Such polar groups have therefore come to be known as osmophoric groups or osmophores,[22] and they are used in structure–activity relationships (SARs) as a molecular reference point.[21,22] (Occasionally, a second, usually weaker, electron donor or acceptor is also involved.) Structures **21**–**24** all contain a cyclohexane ring with an osmophoric group at one end and either an isopropyl or *tert*-

butyl group at the other (Figure 4). In dihydrocryptyl acetate (**21**) and *p-tert*-butylcyclohexyl acetate (**22**), the osmophore is an acetate and there is little effect on the odor upon changing an isopropyl group for a *tert*-butyl substituent; Arctander

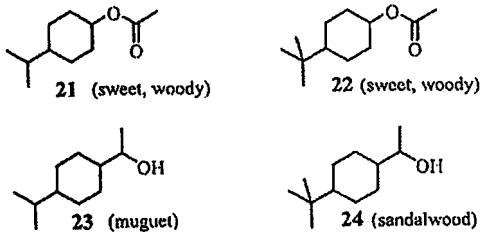


Figure 4. Role of the osmophore.

describes both as being predominantly sweet and woody in character.[24,25] However, when the osmophore is the secondary alcohol group of structures **23** and **24**, a similar small structural change has a major effect on the odor, taking it from muguet to sandalwood.[26]

Similarly, substitution of the *tert*-butyl group of **22** by an isobutyl group to give **25** changes the odor from sweet and woody to a harsh raspberry character,[27] whereas the same exchange has little effect on the muguet character of Lilial (**13**), whose isobutyl analogue Silvial (**26**) has a similar muguet odor (Figure 5).[28]

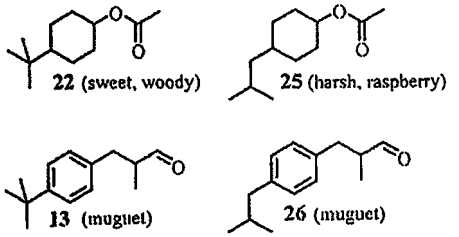


Figure 5. Role of the hydrophobic residue.

Analogous examples also exist in the case of geometric isomers. For instance, in the case of Rossitol, the odor is muguet/citrus whether the alcohol function lies *trans* (**27**) or *cis* (**28**) to the isobutyl group. However, in the analogues in which the isobutyl group has been replaced by a cyclohexyl substituent, the *trans* isomer **29** has a strong, specifically muguet odor whereas that of the *cis* isomer **30** is much weaker, woody, and only generally floral (Figure 6).[29]

The same pattern applies to geometric isomers of double bonds. (*Z*)-4-Heptenal (**31**) has a creamy, buttery odor,[30] whereas the *E* isomer **32** has an aggressive, green and putty-like odor.[31] However, in the case of 2-tetradecenal, both isomers **33** and **34** have fresh, orange odors (although that of **33** is more mandarin-like; Figure 7).[23]

Positional isomers around rings are also subject to this phenomenon. The odor of the *meta* isomer **35** of Lilial (**13**) is reported to be stronger than that of the *para* isomer,[26] whereas the odors of both *m*- and *p*-Cyclamen Aldehydes

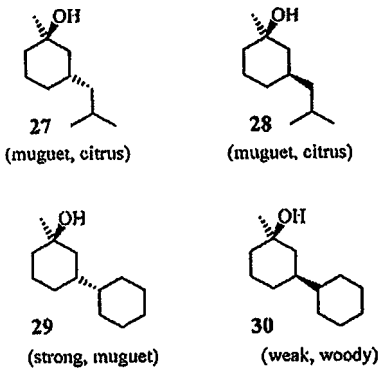


Figure 6. Odors of geometric isomers in rings.

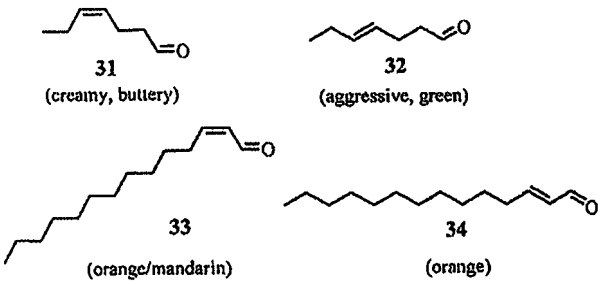


Figure 7. Odors of geometric isomers in olefins.

(**36** and **37**, respectively) are similar in character and intensity (Figure 8).[32] With the dihydrocinnamaldehydes **13** and **35–37**, the intensity of the odor varies but the character of all four remains similar. However, in the case of the acylcyclohexenes **38** and **39**, the shift from *meta* to *para* substitution results in a change in odor character from the green and fatty notes of **38** to the fruity odor of **39** (Figure 8).[33]

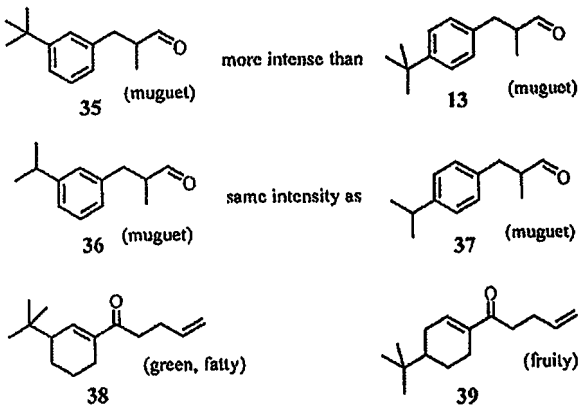


Figure 8. Effect of positional isomers on odor.

The presence or absence of a double bond also provides examples. Linalool (**40**)[34] and dihydrolinalool (**41**)[35] have similar refreshing floral, woody, and citrus odors. However, a similar saturation of a double bond with concomitant

conversion from an allylic alcohol into a saturated alcohol changes the odor from the intense, earthy mushroom character of **42**[11] to the sweet, warm, herbaceous, and nutty scent of **43** (Figure 9).[36]

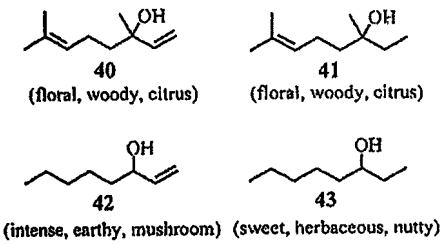


Figure 9. Effect of saturation of a double bond.

The conversion of a primary alcohol into a secondary alcohol by the addition of a methyl group also gives unpredictable results. Geraniol (**44**) is well known for its rosy odor,[37] whereas the higher homologue **45** has an intense fungal odor.[38] On the other hand, a similar transformation from Sandal Mysore Core (Santacore; **46**) to **47**, the dehydro analogue of Sandalore, has only a relatively small effect on the central sandalwood character (Figure 10).[11,39,40]

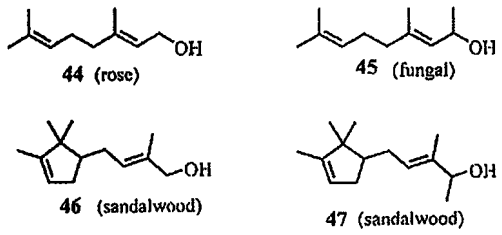


Figure 10. Effect of conversion from primary into secondary alcohols.

As stated above, functional groups are usually important in determining odor character, however, sometimes the exchange of one function for another has little or no effect. In the next three examples, a ketone group is exchanged for the acetate of the corresponding alcohol with three different levels of effect. On going from acetophenone (**48**) to styrallyl acetate (**49**), the odor shifts from sweet hawthorn-like[41] to dry, fruity, and green.[11] On moving from Patchone (**50**) to *p-tert*-butylcyclohexyl acetate (**51**), the degree of change is somewhat less as the odors of both materials have woody characters; that of patchone is very much on the camphoraceous and minty side of wood,[42] whereas the odor of **51** has a sweet, almost fruity character (Figure 11).[25] At the other end of this spectrum, polywood ketone (**52**) and Polywood (**53**) have similar woody, ambergris odors.[23]

Substitutions by a fragment with similar stereoelectronic properties is a common practice in fragrance ingredient discovery, just as it is in drug discovery. For example, when following up on a lead from nature, the isobutenyl group of terpenoid compounds is often substituted by a benzene ring.[43] Thus, citronellol (**54**) served as a lead for Mefrosol (also known as Phenoxanol; **55**) and the odors of both

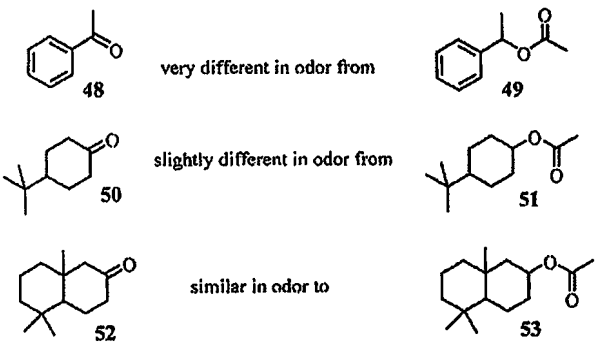


Figure 11. Effect of changing a ketone to an acetate.

compounds have a rosy character.[11] However, the green, pungent, herbaceous character of 2-methylhept-2-ene-6-one (**56**)[44] is not replicated by the sweet, floral character of benzylacetone (**57**; Figure 12).[11]

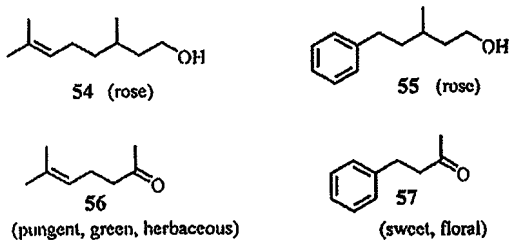


Figure 12. Effect of substitution a fragment with similar stereoelectronic properties.

Another standard substitution is that of a cyclopropane ring for a double bond. The alcohol **46** and ketone **58** both have sandalwood-like odors. Cyclopropanation of both double bonds of **46** produces Javanol (**59**), which is considered to be the strongest sandalwood-scented material known, and both "intermediate" monocyclopropanated species also have predominantly sandalwood characters (Figure 13).[45] However, cyclopropanation of one of the double bonds of **58** to give **60** leads to complete loss of the sandalwood-like odor.[33]

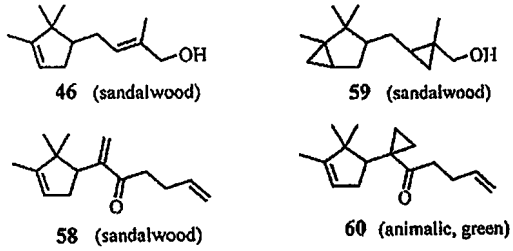
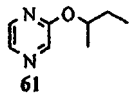


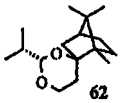
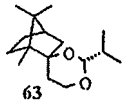
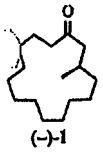
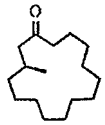
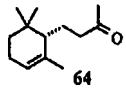
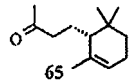
Figure 13. Effect of a cyclopropyl substituent.

Chirality also provides us with many examples of the unpredictability of the effect of changes in molecular structure on the odor of the molecule.[46] In the case of Lilial (**13**) one enantiomer is odorless,[47] whereas the odors of both


61

enantiomers of the pyrazine **61** are identical in character and threshold.[48] The pair of ethers **62** and **63** have identical thresholds of detection but different odor characters (Table 1).[49] The odors of the musks (−)-**1** and (+)-**1** have the same character, but the threshold of (−)-**1** is 0.43 $ng L^{-1}$ whereas that of its enantiomer (+)-**1** is over twenty times higher at 9.5 $ng L^{-1}$.[50] The odors of the enantiomers of dihydro-α-ionone, **64** and **65**, differ in both character and threshold.[51]

Table 1: Effect of chirality on the odor of a molecule.

Compound	Odor	Threshold [$ng L^{-1}$]	Compound	Odor	Threshold [$ng L^{-1}$]
 62	woody, pineapple	40	 63	woody, rose	40
 (−)-1	musk	0.43	 (+)-1	musk	9.5
 64	orris	100	 65	violet	31

Subsequent developments based on the discoveries of Buck and Axel have enabled molecular biologists to extract the genes involved and to incorporate them into cells in culture and therefore to profile the sensitivity of individual receptor types. One interesting outcome of this discovery is that we now know that olfactory receptors are expressed in sites other than the nose and that they serve quite different functions in these other sites. An example of such work was published by Spehr et al.,[58] who showed that the human receptor hOR17-4 (which is found in sperm as well as in the nose) responds to compounds **13**, **37**, and **66–73**, but not to compounds **19** and **74–82** (Figure 14). The strongest response is observed with Bourgeonal (**70**), although this compound is not the natural substrate of the receptor in either the nose or in sperm. To the discovery chemist, this observation points towards a binding site that requires an aldehyde as a hydrogen-bond acceptor and a shape based around that of an alkyl-substituted dihydrocinnamaldehyde. This information can now be used to build a model that could be of use in designing new molecules which could potentially serve as ligands for hOR17-4. One important observation here is that the results confirm that there is not a simple correlation between receptor activity and odor. For example, phenylacetaldehyde (**66**) fires the receptor but its intense green odor[59] is a far cry from the muguet character of Lilial,[11] which is another agonist.

4. Recent Advances in Understanding Odor Perception

In the 15 years since Weyerstahl's review,[23] our ability to predict the odor of a molecule from its molecular structure has not changed much. What has changed, however, is our understanding of why such predictions are so difficult.

The major breakthrough came in 1991 when Buck and Axel identified the gene family that encodes for the olfactory receptor proteins.[52] The proteins belong to the family of seven transmembrane G-protein-coupled receptors (GPCRs) and constitute the largest family in the genome. Eight years later, Buck and co-workers[53] showed that each of the receptors was broadly tuned, in that it responds to a range of odorant molecules and that, conversely, each odorant molecule triggers a range of receptor types. This report confirmed the hypothesis proposed by Polak that the sense of smell works on a combinatorial basis.[54] Buck and Axel received the Nobel Prize in Physiology or Medicine in 2004 for their work,[55] and their accounts were published recently.[56,57] One might expect that such huge advances in our understanding of the initial stages of odor perception would help us to predict the odor of molecules, but they do not. On the contrary, the breadth of receptor tuning and the large number of receptors involved actually explain why it is so difficult and why it will remain so for a very considerable time to come.

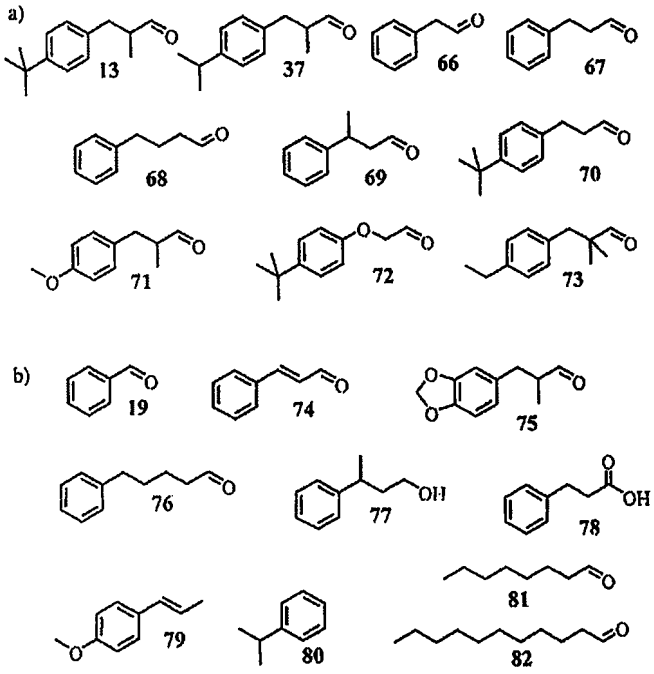


Figure 14. Agonists (a) and non-agonists (b) for hOR-17.

Araneda et al.[60] studied the receptive range of the rat olfactory receptor ORI7. Whereas Spehr et al. carried out direct measurements on the receptor cells, Araneda et al. assessed activity indirectly by measuring activity in the olfactory bulb at the glomerulus which corresponds with receptor neurons that possess ORI7. They found that this receptor responds to certain aliphatic aldehydes. From the degree of binding to 90 different test materials, they were able to establish that the binding site seems to recognize only aldehydes. There seems to be a strong steric restriction close to the aldehyde-binding point but much less strict steric requirements further away from it until a limit is reached at a chain length of 11 carbon atoms. Thus, as with hOR17-4, we can now construct a model to aid in molecular design, in this case with an aldehyde-docking area and a hydrophobic pocket with a specific overall length, and which is slightly broader at the end distant from the aldehyde.

The results described above with ORI7 and hOR17-4 point towards reasonably selective binding sites, whereas those from other receptors are much less clear-cut. For instance, Sanz et al.[61] investigated the specificity of two olfactory receptors, human class I OR52D1 and human class II OR1G1, with rather different results (Table 2). OR1G1 responds strongly to 2-ethylhexan-1-ol (**83**) and to 1-nonanol (**84**) but only weakly to 1-heptanol (**85**) and various isomeric octanols. It reveals a moderate response to decanoic acid (**86**) but no response to octanoic acid (**87**) and only a weak one to nonanoic acid (**88**). In the aldehyde series, its strongest response is to nonanal (**89**). With octanal (**81**) and decanal (**90**) it elicits only weak responses, whereas with benzaldehyde (**19**) and Lyral (**91**) it responds moderately. Of 16 esters tested, OR1G1 responds strongly only to ethyl isobutyrate (**92**); its response to the isomeric ethyl butyrate (**93**) is only weak and that to butyl butyrate (**94**) is almost zero. Strong responses were also observed to molecules as diverse as methyl thiobutanoate (**95**), benzothiazole (**96**), and γ-undecalactone (**97**). Thus OR1G1 seems to be quite selective *within* a class of substrates (for example, alcohols or acids) but not selective *between* classes, as it responds to alcohols, aldehydes, acids, esters, lactones, and a variety of heterocyclic systems. On the other hand, receptor OR52D1 generally responded more weakly to the materials in the same test set of 100 but with a different and equally puzzling pattern. It is difficult to see how one might design a model for a typical substrate for either of these receptors.

Research based on Buck and Axel's work has revealed the primary sequences of all of the human olfactory receptor proteins and now allows us to determine which are expressed in any individual. However, these proteins are proving difficult to work with experimentally and none have yet been

Table 2: Response of OR1G1 receptor to various odorant substrates.

	Response		
strong	moderate	weak	none
83, **84**	**86**, **19**, **91**	**85**, **88**, **81**, **90**, **93**	**87**, **89**, **92**, **94**, **95**, **96**, **97**

isolated in pure form. Model studies are based on extrapolation from the structure of bovine rhodopsin, which is the only GPCR for which an X-ray crystal structure exists. There are a number of assumptions in this extrapolation that must be borne in mind. Rhodopsin is an unusual GPCR in several ways, most significantly in that it requires a cofactor, 11-(*Z*)-retinal. There is also an assumption about conservation of tertiary structure from the crystalline environment to the membrane environment in which it is active. The putative binding sites in olfactory receptors are based on the binding site of 11-(*Z*)-retinal in rhodopsin rather than on in vivo experimental evidence. Spehr et al.[58] showed that activation of hOR-17 by Bourgeonal (**70**) is inhibited by undecanal (**82**), a non-agonist, and this result might suggest allosteric interactions and hence multiple binding sites. The role of odor-binding proteins (OBPs) in the olfactory mucosa is not understood and it is not known for certain whether or not they play an active role in olfaction or serve merely to remove excess odorant. However, work such as that of Spehr et al.[58] shows that, in the case of sperm or HEK cells, the receptor can be fired without the presence of an OBP.

Nonetheless, some excellent work is being done on building models of putative receptor sites and correlating these with in vivo activity. The work of Goddard and co-workers[62–64] serves as an illustration. Such work nicely complements the substrate-modeling approach of traditional SAR models.

Traditional SAR and binding-site models are essentially static in nature. A recent paper by Lai et al.[65] suggests that this might not be the best approach. Like Araneda et al.,[60] they looked at rat ORI7 receptors. Lai et al. generated a computer model of the receptor and fitted models of potential ligands into the putative binding site. They then set the whole assembly into normal motion and observed whether or not the ligand remained in the binding pocket. Molecules **81** and **98–102** remained in the binding site, whereas **103** and **104** moved out of the pocket once vibratory motion started (Figure 15). This model correlates with experiment as **81** and **98–102** are all activators in vivo whereas 103 and **104** are not. These results suggest that dynamics should be considered in addition to the traditional static stereoelectronic space-fitting approach. Prediction of new structures would be more difficult using a dynamic model and its use as an in silico screen prior to in vivo evaluation would seem more likely.

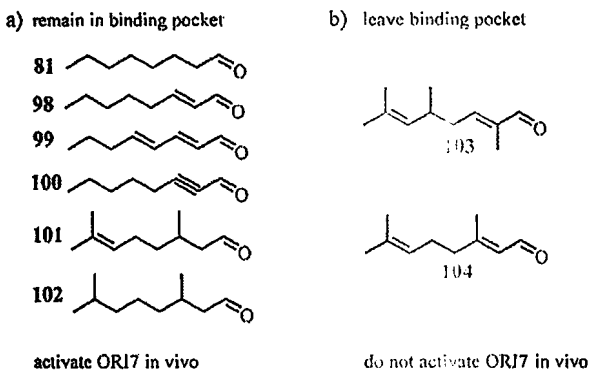


Figure 15. Results of dynamic modeling of ORI7.

5. Summary and Outlook

From all of the above examples, it is clear that even when the structure of an olfactory receptor is known it is far from certain that one could predict how well any novel potential ligand would bind to it. Facing an array of 350–400 receptors, the task would be even more difficult as a subtle change in structure might affect the binding of any one of the receptors which even a close analogue activates. In other words, the chances of correctly predicting the total pattern of receptor signaling for an odorant molecule are hundreds of times less than doing so for a pharmaceutical target. Furthermore, there are many levels of neurotransmission between the receptors and the cortex, where the signals from the receptor array are eventually interpreted as the phenomenon that we refer to as odor. At each level there are gates with opportunities for interaction between signals from different receptors and the possibility for either reduction or enhancement of individual signal components. All of this would have to be understood in order to know how the initial signal pattern would come together in the higher brain. A subtle change in signal intensity from one receptor type could have a disproportionately large effect on the overall interpretation in terms of odor character, threshold, and/or perceived intensity.

It would therefore seem that consistently accurate prediction of odors will not be possible for a very considerable time and not until a great amount of further research has been completed, the cost of which could not be borne by the flavor and fragrance industry.

In his review, Weyerstahl[23] outlined the objectives of structure–odor correlations as being 1) prediction of odors, 2) rational design of odorants, and 3) understanding the mechanism of olfaction. Since then, advances in the biosciences have greatly increased our understanding of the mechanism of olfaction but in a way that does not bode well for Weyerstahl's other two objectives. It would appear that our SAR tools will be refined and improved, although, for the foreseeable future, the prediction of odor will remain only statistical probabilities rather than certainties. There will be plenty of room for surprises and serendipity.

I would like to thank my colleagues Richard Butcher, Dr. Karen Jenner, Dr. Keith Perring, and Dr. Anton van der Weerdt for their help in preparing the manuscript.

Received: February 28, 2006

[1] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 2276.
[2] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 2279.
[3] P. C. Traas, H. Renes, H. Boelens (Naarden International), US 4,352,748, **1982**.
[4] A. Boix Camps, *Perfum. Flavor.* **2004**, *29*, 42–65.
[5] G. Ohloff, W. Giersch, W. Thommen, B. Willhalm, *Helv. Chim. Acta* **1983**, *66*, 1343–1354.
[6] C. S. Sell, *Seifen Öle Fette Wachse* **1986**, 112 (8), 267–270.
[7] T. Asada, Y. Ataka, J. Etsuno, H. Takase (Kao Corporation), JP 09151164, **1997**.

[8] A. Boix Camps, *Perfum. Flavor.* **1999**, *24*, 17–47.
[9] J. E. Amoore in *Molecular Basis of Odour*, Charles C. Thomas, Illinois, **1970**, Library of Congress Card No. 70-97521.
[10] P. Z. Bedoukian, *Perfumery Synthetics and Isolates*, D. van Nostrand, New York, **1951**, p. 43.
[11] H. Surburg, J. Panten, *Common Fragrance and Flavor Materials*, 5th ed., Wiley-VCH, Weinheim, **2006**.
[12] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 753.
[13] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 268.
[14] S. Arctander, *Perfume and Flavor Materials of Natural Origin*, S. Arctander, Elizabeth, New Jersey, **1960**.
[15] M. H. Klouwen, *Perfum. Essent. Oil Rec.* **1959**, 27–33.
[16] C. S. Sell, *Chem. Br.* **1997**, *3*, 39–42.
[17] K. J. Rossiter, *Chem. Rev.* **1996**, *96*, 3201–3240.
[18] M. Chastrette, J. Y. De Saint Laumer, *Eur. J. Med. Chem.* **1991**, *26*, 829–833.
[19] I. B. Bersuker, A. S. Dimoglo, M. Yu. Gorbachov, P. F. Vlad, M. Pesaro, *New J. Chem.* **1991**, *15*, 307–320.
[20] "The Measuring of Odour": N. Neuner-Jehle, F. Etzweiler in *Perfumes: Art, Science and Technology* (Eds.: P. M. Müller, D. Lamparsky), Elsevier, London, 1991, pp. 153–212.
[21] P. Kraft, W. Eichenberger, *Eur. J. Org. Chem.* **2003**, 3735–3743.
[22] P. Kraft in *Chemistry and Technology of Flavors and Fragrances* (Ed.: D. J. Rowe), CRC, Boca Raton, **2005**, pp. 143–168.
[23] P. Weyerstahl, *J. Prakt. Chem.* **1994**, *336*, 95–109.
[24] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 2693.
[25] S Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 440.
[26] "Synthesis of New Floral Fragrances Supported by Molecular Modelling": R. Pelzer, U. Harder, H. Krempel, H. Sommer, H. Surburg, P. Höver in *Recent Developments in Flavour and Fragrance Chemistry, Proceedings 3rd International H&R Symposium* (Eds.: R. Hopp, K. Mori), VCH, Weinheim, **1993**, pp. 29–67.
[27] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 437.
[28] A. Boix Camps, *Perfum. Flavor.* **2004**, [illegible], 54–80.
[29] K. J. Rossiter (Quest International), U[illegible]6,313,187, **2001**.
[30] P. Haverkamp-Begemann, J. C. Koster, *Nature* **1964**, *202*, 552–553.
[31] S. K. Mukerji, H. L. Sharma, *Tetrahedron Lett.* **1966**, *7*, 2479–2481.
[32] W. Berends, L. M. van der Linde, *Perfum. Essent. Oil Rec.* **1967**, (June), 372–378.
[33] J. A. Bajgrowicz, K. Berg-Schultz, G. Brunner, *Bioorg. Med. Chem.* **2003**, *11*, 2931–2946.
[34] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, 1969, Monograph 1s
[35] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 160.
[36] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 2402.
[37] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 1426.
[38] W. Czeslaw, A. Zabra, *Perfum. Flavor.* **1983**, *8*, 39–47.
[39] R. E. Naipawer, W. M. Easter (Givaudan), US 4,052,341, **1977**.
[40] R. E. Naipawer (Givaudan), EP 203,528, **1986**.
[41] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 24.
[42] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 436.
[43] W. Sturm, *Parfuem. Kosmet.* **1974**, *55*, 351–355.
[44] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 2043.
[45] J. A. Bajgrowicz, I. Frank, G. Fráter, M Hennig, *Helv. Chim. Acta* **1998**, *81*, 1349–1358.
[46] C. S. Sell, *Chem. Biodiversity* **2004**, *1*, 1899–1920.
[47] D. Bartschat, S. Börner, A. Mosandl, J. W. Bats, *Z. Lebensm.-Unters.-Forsch. A* **1997**, *205*, 76–79.
[48] M. Masuda, S. Mihara, *Agric. Biol. Chem* **1989**, *53*, 3367–3368.
[49] J. A. Bajgrowicz, I. Frank, *Tetrahedron: Asymmetry* **2001**, *12*, 2049–2057.
[50] C. Fehr, J. Galindo, O. Etter, *Eur. J. Org. Chem.* **2004**, 1953–1957.
[51] E. Brenna, C. Fuganti, S. Serra, P. Kraft, *Eur. J. Org. Chem.* **2002**, 967–978.
[52] L. Buck, R. Axel, *Cell* **1991**, *65*, 175–187.
[53] B. Malnic, J. Hirono, T. Sato, L. B. Buck, *Cell* **1999**, *96*, 713–723.
[54] E. H. Polak, *J. Theor. Biol.* **1973**, *40*, 469–484.
[55] http://nobelprize.org/nobel prizes/medicine/.
[56] R. Axel, *Angew. Chem.* **2005**, *117*, 6264–6282; *Angew. Chem. Int. Ed.* **2005**, *44*, 6111–6127.
[57] L. B. Buck, *Angew. Chem.* **2005**, *117*, 6283–6296; *Angew. Chem. Int. Ed.* **2005**, *44*, 6128–6140.
[58] M. Spehr, G. Gisselmann, A. Poplawski, J. A. Riffell, C. H. Wetzel, R. K. Zimmer, H. Hatt, *Science* **2003**, *299*, 2054–2058.
[59] S. Arctander, *Perfume and Flavor Chemicals*, S. Arctander, Montclair, New Jersey, **1969**, Monograph 2470.
[60] R. C. Araneda, A. D. Kini, S. Firestein, *Nat. Neurosci.* **2000**, *3*, 1248–1255.
[61] G. Sanz, C. Schlegel, J.-C. Pernollet, L. Briand, *Chem. Senses* **2005**, *30*, 69–80.
[62] P. Hummel, N. Vaidehi, W. B. Floriano, S. E. Hall, W. A. Goddard III, *Protein Sci.* **2005**, *14*, 703–710.
[63] S. E. Hall, W. B. Floriano, N. Vaidehi, W. A. Goddard III, *Chem. Senses* **2004**, *29*, 595–616.
[64] W. B. Floriano, N. Vaidehi, W. A. Goddard III, *Chem. Senses* **2004**, *29*, 269–290.
[65] P. C. Lai, M. S. Singer, C. J. Crasto, *Chem. Senses* **2005**, *30*, 781–792.

2'-hydroxyacetophenone

Select Language

Powered by Google Translate

1-(2-hydroxyphenyl)ethanone (Click)
IUPAC Name :1-(2-hydroxyphenyl)ethanone
Std.InChI :InChI=1S/C8H8O2/c1-6(9)7-4-2-3-5-8(7)10/h2-5,10H,1H3
InChI :InChI=1/C8H8O2/c1-6(9)7-4-2-3-5-8(7)10/h2-5,10H,1H3
Std.InChIKey :JECYUBVRTQDVAT-UHFFFAOYSA-N
InChIKey :JECYUBVRTQDVAT-UHFFFAOYAR
SMILES :CC(=O)C1=CC=CC=C1O

CAS Number :	118-93-4
ESIS EC# (EINECS) :	204-288-0
Beilstein Number :	0386123
FEMA Number :	3548
COE Number :	11784
XlogP3 :	1.90 (est)
Molecular Weight :	136.1479200
Formula :	C8 H8 O2
NMR Predictor :	Predict
Category :	flavor and fragrance agents

US / EU / EUROPA / FDA / JECFA Information :

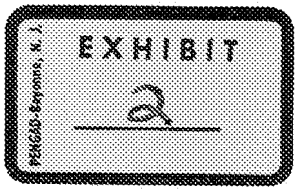
<Suppliers> <Organoleptics> <Properties> <Safety> <Safety in use> <Safety references> <References> <Other> <Top>

Google Scholar :	Search	Google Books :	Search
Google Patents :	Search	US Patents :	Search
EU Patents :	Search		
PubMed :	Search	NCBI :	Search
JECFA Food Flavoring :	2-Hydroxyacetophenone		
Fl@vouring Number :	07.124		
FDA Mainterm :	2-HYDROXYACETOPHENONE		

Suppliers :

<EU/US> <Organoleptics> <Properties> <Safety> <Safety in use> <Safety references> <References> <Other> <Top>

Aceto :	2'-Hydroxyacetophenone



2'-hydroxyacetophenone

Select Language

Powered by Google Translate

Penta :	**2-hydroxyacetophenone**
SAFC Global :	**2'-Hydroxyacetophenone ≥98% Odor: hawthorne; herbaceous; sweet**
Organoleptics :	
<Suppliers> <EU/US> <Properties> <Safety> <Safety in use> <Safety references> <References> <Other> <Top>	
Odor Type :	**phenolic**
Odor Strength :	**medium , recommend smelling in a 10.00 % solution or less**
Odor Description: at 10.00 % in dipropylene glycol.	**phenolic sweet hawthorn tobacco honey herbal** Luebke, William tgsc, (1987)
Odor Description: at 2.00 %.	**Phenolic, sharp, benzaldehyde, cherry pit, tropical, melon with a tobacco afternote** Mosciano, Gerard P&F 23, No. 5, 49, (1998)
Taste Description: at 5.00 ppm.	**Naphthyl, cinnamon, cherry pit, coumarin, phenolic, tobacco and honey** Mosciano, Gerard P&F 23, No. 5, 49, (1998)
Substantivity :	**360 Hour(s)**

2-hydroxybenzaldehyde

Select Language — Powered by Google Translate

2-hydroxybenzaldehyde (Click)
IUPAC Name :2-hydroxybenzaldehyde
Std.InChI :InChI=1S/C7H6O2/c8-5-6-3-1-2-4-7(6)9/h1-5,9H
InChI :InChI=1/C7H6O2/c8-5-6-3-1-2-4-7(6)9/h1-5,9H
Std.InChIKey :SMQUZDBALVYZAC-UHFFFAOYSA-N
InChIKey :SMQUZDBALVYZAC-UHFFFAOYAD
SMILES :C1=CC=C(C(=C1)C=O)O

CAS Number :	90-02-8
ESIS EC# (EINECS) :	201-961-0
Beilstein Number :	0471388
FEMA Number :	3004
COE Number :	605
XlogP3 :	1.80 (est)
Molecular Weight :	122.1213400
Formula :	C7 H6 O2
Pherobase Floral:	View
NMR Predictor :	Predict
Category :	flavor and fragrance agents

US / EU / EUROPA / FDA / JECFA Information :

<Suppliers> <Organoleptics> <Properties> <Safety> <Safety in use> <Safety references> <References> <Cosmetics> <Other> <Top>

Google Scholar :	Search	Google Books :	Search
Google Patents :	Search	US Patents :	Search
EU Patents :	Search		
PubMed :	Search	NCBI :	Search
JECFA Food Flavoring :	Salicyladehyde		
FI@vouring Number :	05.055		
FDA Mainterm :	SALICYLALDEHYDE		
FDA Regulation. :	FDA PART 172 -- FOOD ADDITIVES PERMITTED FOR DIRECT ADDITION TO FOOD FOR HUMAN CONSUMPTION Subpart F--Flavoring Agents and Related Substances Sec. 172.515 Synthetic flavoring substances and adjuvants.		

Suppliers :

<EU/US> <Organoleptics> <Properties> <Safety> <Safety in

EXHIBIT 13

2-hydroxybenzaldehyde	Select Language Powered by Google™ Translate

Aceto :	Salicylaldehyde
Berje :	Salicylaldehyde
Penta :	salicylaldehyde
SAFC Global :	Salicylaldehyde ≥98%, Kosher Odor: almond; spicy

Organoleptics :

Odor Type :	medicinal
Odor Strength :	medium , recommend smelling in a 10.00 % solution or less
Odor Description: at 10.00 % in dipropylene glycol.	medical spicy cinnamon wintergreen cooling
Odor Description:	Medicinal, spicy cinnamon-wintergreen like cooling note Mosciano, Gerard P&F 16, No. 2, 49, (1991)
Taste Description: at 20.00 ppm.	Spicy, medicinal and astringent Mosciano, Gerard P&F 16, No. 2, 49, (1991)